



Wyeth Pharmaceuticals

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Section 3.2.2.2.1

Venlafaxine Administration to Healthy Subjects

summarized from studies 0600B1-144-FR (GMR-26761), The Absolute Bioavailability and EEG Effects of Conventional and Extended Release Venlafaxine in Healthy Volunteers, and 0600B1-208-US (GMR-26165), A Double-blind, Placebo-Controlled Study of Venlafaxine and Venlafaxine ER in Outpatients With Major Depression.

3.2.2.2.1 Venlafaxine Administration to Healthy Subjects

3.2.2.2.1.1 Study 144 - Design

Study 144 was a randomized, double-blind, placebo-controlled, 4-period crossover, single-dose study. This study was conducted at a single center with 16 healthy male subjects between 18 and 27 years of age.

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Each subject received 1 of the 4 treatments during each of 4 study periods:

- Placebo
- Venlafaxine ER 75 mg
- Venlafaxine IR 50 mg
- Venlafaxine intravenous (IV) 10 mg

Data for quantitative electroencephalography (Q-EEG) were collected before dose administration (0 hours) and at discrete time interval up to 34 hours after administration of study medication. Four (4) EEG leads (according to the international 10-20 system) were recorded for 5 minutes under resting conditions in a quiet room, with dimmed lighting ; the subjects were lying in bed with their eyes closed. This type of EEG recording is more sensitive in measuring pharmacodynamic effects such as onset, duration, and peak of activity than EEG recordings under vigilance-controlled conditions.

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Data for the visual analog scales (VAS) for nausea (100 mm long) were collected before dose administration (0 hour) and at discrete time intervals up to 48 hours after administration of study drug. The VAS ratings were analyzed over time and formulations by using the absolute value and a normalized ratio.

3.2.2.2.1.2 Safety Results

3.2.2.2.1.2.1 Nausea

3.2.2.2.1.2.1.1 Incidence of Nausea

Overall, the incidence of nausea was lowest with the ER formulation and was the highest with the IV formulation (Table 3.2.2.2.1.2.1.1A). Most of the adverse events in this study were nausea.

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TABLE 3.2.2.2.1.2.1.1A. NUMBER (%) OF PATIENTS WITH TREATMENT-EMERGENT NAUSEA BY TREATMENT

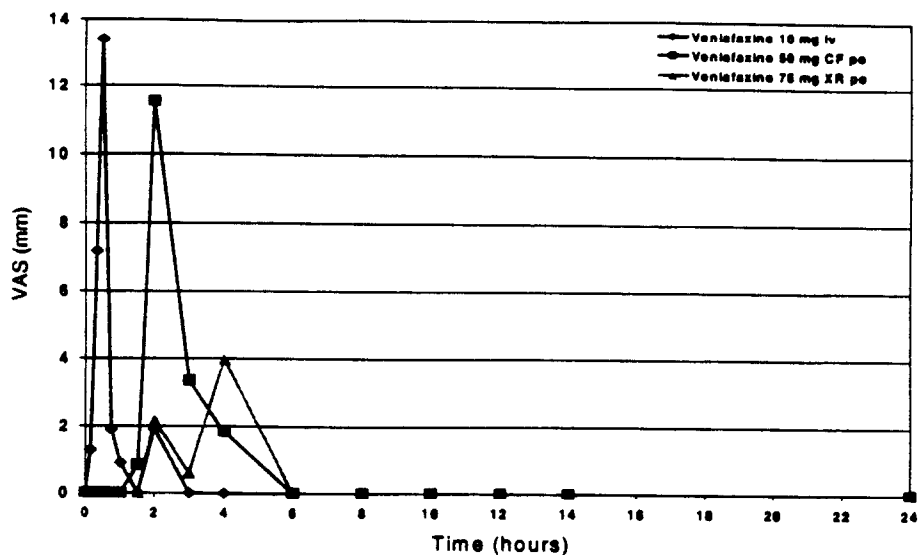
Adverse Event	Placebo	Venlafaxine ER	Venlafaxine IR	Venlafaxine IV
Any event	1 (6)	8 (50)	9 (56)	13 (81)
Nausea	1 (6)	6 (38)	8 (50)	11 (69)

3.2.2.2.1.2.1.2 Severity of Nausea

The severity of nausea was assessed at different time points after administration of venlafaxine using a VAS (Figure 3.2.2.2.1.2.1.2A).

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FIGURE 3.2.2.2.1.2.1.2A. TIME COURSE OF NAUSEA SEVERITY AFTER VENLAFAXINE ADMINISTRATION



CF = conventional formulation (IR); XR = Extended release formulation (ER)

The time to peak of nausea severity was not significantly different between venlafaxine IR (2.36 ± 0.22 hours) and ER (3.10 ± 0.27 hours), but the times for both were significantly different from that for venlafaxine IV (0.23 ± 0.15 h) (Table 3.2.2.2.1.2.1B).

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For each of the 3 venlafaxine formulations, the time to peak of nausea severity occurred before the time of peak (t_{max}) plasma concentration (Table 3.2.2.2.1.2.1.2A), suggesting that the occurrence of nausea is related more to the rate of increase of venlafaxine concentration than to its peak.

TABLE 3.2.2.2.1.2.1.2A. RELATION BETWEEN THE TIME TO VENLAFAXINE PLASMA PEAK CONCENTRATION (t_{\max}) AND THE TIME TO PEAK OF NAUSEA SEVERITY (N_{\max})

Treatment	N_{\max} (h)	t_{\max} (h)
Venlafaxine		
10 mg IV	0.23 ± 0.15	0.5 ± 0.1
50 mg IR q12h	2.36 ± 0.22 *	2.8 ± 0.8
75 mg ER q24h	3.10 ± 0.27 *	5.8 ± 1.6

* $p < 0.05$ when compared with venlafaxine 10 mg IV

The severity of nausea was markedly reduced with the venlafaxine ER formulation compared with that seen with the IR formulation.

Expressed in dose-normalized area under the curve (AUC/dose, mm•s/mg), the AUC/dose of nausea was reduced by 63% after venlafaxine ER was administered when compared with venlafaxine IR (Table 3.2.2.2.1.2.1.2B).

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TABLE 3.2.2.2.1.2.1.2B. AREA UNDER THE CURVE FOR THE VISUAL ANALOG SCALE (NAUSEA)

Treatment	AUC (mm•s)	AUC/Dose (mm•s/mg)	% Change from IR of AUC/Dose
Venlafaxine 10 mg IV	23212	2321	+105
Venlafaxine IR 50 mg	56418	1128	ND
Venlafaxine ER 75 mg	29643	395	-63

Abbreviation: AUC = area under the curve; mm = millimeters; s = seconds.

Thus, the severity of nausea is lower with venlafaxine ER than with venlafaxine IR, although the incidence of nausea is not markedly reduced with the venlafaxine ER formulation.

In contrast, the IV administration of venlafaxine induced an increase of 105% in the magnitude of nausea severity when compared with venlafaxine IR.

3.2.2.2.1.2.2 Vomiting

There was no difference in the incidence of vomiting related to the formulation of venlafaxine used.

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One (1) patient had vomiting with each venlafaxine formulation (ER, IR, IV).

3.2.2.2.1.3 Central Effects of Venlafaxine

Q-EEG was used to compare the CNS effects of the venlafaxine IR and ER formulations.

All the EEG recordings were performed in a quiet room, with dimmed lighting; the subjects were lying in bed with their eyes closed under resting conditions. This type of EEG recording was more sensitive in measuring pharmacodynamic effects such as onset, duration, and peak of activity than EEG recordings under vigilance-controlled conditions.

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The results of the study demonstrated that the main EEG modifications produced by venlafaxine, whatever the formulation, were an increase in fast beta energies in the frontotemporal leads.

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The effects of venlafaxine IR peaked between 10 and 14 hours and those of venlafaxine ER, between 12 and 24 hours for most parameters.

Further, the analysis of the AUC of the EEG parameters showed that there were no significant differences between venlafaxine IR and ER formulations, regardless of the EEG lead or parameter employed.

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There was therefore no evidence of a decrease in the central activity of the ER formulation compared with the IR formulation.

3.2.2.2.1.4 Safety Review of Other Phase 1 Studies

Table 3.2.2.2.1.4A summarizes the nausea incidence in those phase 1 studies in which there was a direct comparison of venlafaxine IR and

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